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Review Article

Screening and Prevention of Cervical Cancer in the World

Abstract

Cervical cancer is the leading cause of morbidity and mortality among gynecological cancers worldwide. Cervical cancer is the main cancer found in developing countries. There are risk factors for cervical cancer worldwide, mainly persistent infection of high risk HPV, especially genotypes 16 and 18 viruses. Cervical cancer prevented when precursor lesions detected and treated before they develop cancer. Cervical cancer is preventable, and effective screening programs reduce morbidity and mortality associated with this type of cancer; however, the programs vary according to socio-economic conditions of each country, which reflected in the increased incidence, morbidity, mortality from cervical cancer in developing countries.

Introduction

Cervical cancer is the second most common cancer in the world, with 528,000 new cases and 266,000 deaths in women each year [1], Occurs in 85% of women and 87% of those who die are in emerging or middle income countries [1]. Women with HIV are at increased risk of developing cervical cancer with increased disease progression. Since 1993, CaCu has been classified as a disease defining AIDS [2]. The World Health Organization (WHO) advocates a comprehensive approach to prevention and control of CaCu to identify opportunities for effective interventions [3,4]. In 2012, represents 12% of all gynecological cancers. The highest risk regions, in excess of 30 per 100,000 people per year, include East Africa (42.7), Melanesia (33.3), South (31.5) and Middle (30.6) Africa. Rates are lowest in Australia / New Zealand (5.5) and West Asia (4.4). Cervical cancer remains the most common cancer in eastern and central Africa, accounting for 7.5% of all gynecological cancer deaths, nine out of ten (87%) cervical cancer deaths occur in emerging countries, and mortality varies 18 times in different regions of the world, with rates ranging from less than 2 per 100,000 in Western Asia, Western Europe and Australia / New Zealand to over 20 per 100,000 in Melanesia (20.6), Middle (22.2) and East (27, 6) Africa [5]. The incidence and mortality are related to poverty, limited access to health care, life in rural areas and low levels of education access; Several studies have documented disparities in relation to the incidence, screening coverage, treatment, survival and mortality compared with developed countries; where the evidence shows that marginalized populations, social, geographic and economic terms, are more likely to die from

cervical cancer, which is attributed, among other factors we do not receive a timely diagnosis and treatment is delayed [6,7]. In Mexico, as in other developing countries, a high incidence and mortality from cervical cancer that arises linked by social inequality, which relates to the place of residence, ethnicity, socioeconomic status and access to social security records, among other factors [6,7].

Cervical cancer is the main cancer found in developing countries there risk factors for cervical cancer worldwide; mainly persistent infection by human papillomavirus (HPV) high-risk (HPV-hr), especially HPV-16 and HPV-18 virus. Cervical cancer prevented when precursor lesions detected and treated before it develops this. Cervical cancer is preventable, and effective screening programs reduce morbidity and mortality associated with this cancer. Cervical cancer prevention includes primary, secondary and tertiary prevention. Primary prevention is avoiding exposure to risk factors and vaccination; secondary prevention means detect precancerous disease and provide treatment. Tertiary prevention includes measures to reduce the recurrence or progression to invasive disease or palliative measures [6,7]. Worldwide, cervical cancer is the second most common cancer in women worldwide after breast cancer. This is the most important cancers that kill women in developing countries [3,8], where 83% of new cases and 85% of deaths from cervical cancer reported in developing countries; which is a public health problem in these countries and the main reason is the limited access to screening and treatment access. In Southeast Asia, the age-standardized incidence varies from 10 per 100,000 women in Hong Kong and Singapore, 20 per 100,000 women in Malaysia, the Philippines, Thailand

and Vietnam [4,9]. In Europe, the incidence rates of cervical cancer are not proportional across the continent in general; the incidence is 10.6 per 100,000. In Western Europe, the incidence rate is lower than in Central and Eastern Europe. The low rate in Western Europe is the development of prevention programs; HPV vaccination; these programs have not been implemented in countries with higher incidence. To control the problem of cervical cancer in Europe is based on programs providing public health care [6,10], but in developing countries, prevention is a challenge; where only 5% of women will be enhanced based on cytology screening in a period of five years; secondary to the lack of availability of qualified and trained professionals to effectively implement a program of this type; besides the health funds are not available to maintain a program of this type. In developing countries, many of the problems in screening programs based on cytology, countries is the poor distribution of preventive services where only hospitals or private laboratories perform them; addition, the delay in reporting the results of cytology and patients may not have affected the results, and no treatment or monitoring [6,7].

Natural history of the disease

The natural history of cervical cancer is the result of the progression of mild dysplasia or cervical intraepithelial neoplasia (CIN) grade-1 to moderate to severe dysplasia and in situ or CIN-2 and CIN-3 carcinoma; some of these pre-invasive lesions or CIN return to normal, but a proportion will become cervical cancer in 10 to 15 years. The CIN-2/3 known as high-grade squamous lesions (HSIL), which maintain for a long time and are detected during screening and treated before progression to cancer. In recent decades, this strategy has decreased the morbidity and mortality from cervical cancer in developed countries [7,11].

Risk factors

Hr-HPV is the main risk factor for cervical cancer and increased with increasing number of sexual partners; others include smoking, young age at first intercourse and first pregnancy, multiparity, prolonged, or more than 5 years of oral contraceptive use. Women previously treated for any CIN, CIN-3 are mainly 2-3 times greater risk of future cervical cancer, but no increased risk of dying from this [8,12]. HPV infection at the early age of first intercourse, multiple sexual partners and smoking are the main risk to develop it [7,11]. Sexual intercourse at an early [13] age before age 17, exposes women to semen that is potentially carcinogenic, besides the cervical epithelium is more susceptible to carcinogens during adolescence and early age to start sexual life and pregnancy are risk factors for cervical cancer; even when reusing pads, it is also a risk factor [7,11]. Smoking (in the form of chewing or smoking) correlates with HPV infection and malignant lesions of the oral cavity and smoking is associated with the development of CIN and cervical cancer [7,11]. Smoking an environmental cofactor influencing the risk of cervical cancer, with double the risk for current smokers compared with non-smokers and risk factors associated with persistent HPV infection include smoking, immunosuppression, early age at onset of sexual life, multiparity, prolonged use of hormonal

contraceptives and sexually transmitted infections; current smoking increases the risk of cervical cancer in women positive squamous type HPV, which is greater risk in current smokers than former smokers [7,12].

Obesity not only have a higher risk of developing cancer, mortality also increased by the increase in body mass index (BMI). Obesity is a risk factor for various cancers including breast and endometrial cancer, colon and rectum, esophagus, kidney, pancreas, gall bladder, ovary, and liver cancer [7,11].

There is a relationship between higher parity and cervical cancer compared with nulliparous women, women who have had three or four deliveries term pregnancies have 2.6 times the risk of developing it, women with seven or more births had 3.8 times the risk. In addition, HPV-infected women who had seven or more pregnancies to term delivery have four times the risk of squamous cell cervical cancer compared with nulliparous women and two to three-fold increased risk compared with women who had one or two births pregnancy term. Long-term use of oral contraceptives increases the risk of cervical cancer; HPV-infected women who used oral contraceptives for 5 to 9 years are three times higher incidence and use for 10 years or more increases the risk fourfold. Therefore, changes in lifestyle, such as quitting smoking and reducing the number of sexual partners, can help reduce the risk of cervical cancer [7,11].

Women infected with the Human immunodeficiency virus (HIV) infected more easily with high-risk genotypes and are more likely to develop than HIV negative women of the same age are precancerous lesions. The co-infected women with HPV or other sexually transmitted infection such as chlamydia trachomatis or herpes simplex type 2 (HSV-2) infection, are more likely to develop it and the effect of HSV-2 has increased risk in women positive [7,11], HPV.

Socioeconomic status is a risk factor for many health problems, including cervical cancer, especially in low-income countries; due to restricted access to health services, low-income, malnutrition, and low educational level, lower awareness of health problems and preventive behaviors; these factors make them more vulnerable to disease and preventable infections, such as cervical cancer. Practices or inadequate hygienic conditions increase the risk of HPV infection and cervical Cancer without having enough evidence to support this claim [7,11,12].

Primary prevention

The reduction in exposure to risk factors associated with persistent HPV infection is the necessary cause for cervical cancer; eliminated by preventing HPV infection; although there are many ways for the transmission of HPV infection, sexually and some autoinoculation lock HPV infection by antibodies to L1 and L2 of HPV [12-17]. In episomal state in the host cell, expressing the HPV genome encoded by the E1 and E2 protein regions and E6 and E7. In productive infections, HPV remains episomal state, but in squamous intraepithelial lesions (SIL) or cancers, the HPV genome integrates into the

host genome and integration into the host this leads to changes in gene expression that result in deregulation positive E6 and E7 proteins, which are required for oncogenic transformation of infected cells; HPV infection in neutralizing antibodies to these proteins block new infections with the same genotypes containing HPV vaccines [14-17].

HPV vaccine

In the prophylactic vaccine, the empty viral capsids called viral particles (VLPs) synthesized from microbial systems or cell expression; HPV vaccines well tolerated and generate high levels of antibodies against the HPV genotypes they contain; the most common HPV genotypes associated with cervical cancer are HPV-16 and HPV-18, which account for more than 70% of cervical cancer. HPV vaccines currently considered effective and effective for the prevention of infection and HPV-associated diseases. Three HPV vaccines are currently available: bivalent [14], tetravalent [15], and nonavalent [16,18].

The bivalent vaccine consists of VLPs from genotypes 16 and 18, the tetravalent vaccine, contains VLPs from HPV-16, 18, 6 and 11 genotypes. The last vaccine developed is the non-viral vaccine, which includes VLPs 9 genotypes of HPV- 16, 18, 6, 11, 31, 33, 45, 52 and 58, with the cervical cancer preventive potential [18-20], of 90%.

The recommended vaccination guidelines depend on the type of vaccine, age and immune status. Generally, HPV vaccines administered intramuscularly into the deltoid. These vaccines not indicated in children under 9 years due to lack of immunogenicity and safety studies. In people with immunosuppression, it is recommended to always use the 3 doses regimen, regardless of age. In no case, so far, is the need to administer booster doses. HPV vaccines prevent HPV infection (prophylactic efficacy) but do not modify the natural history of ongoing infections by HPV genotypes included in vaccines (non-therapeutic), the preventive potential is greatest when applied to people Not exposed to HPV; Have significant cross-protection against HPV-31, 33 and 45 genotypes with bivalent vaccine [14], and HPV-31 genotype with tetravalent [15], genotype.

The bivalent vaccine is withdrawn from the United States market. Nonvalent vaccine, soon to replace the tetravalent vaccine, is given in a series of three 0.5 ml injections for 6 months; Currently two doses of HPV vaccine administered with 6 months of separation in individuals aged 9-14 years resulted in antibody titers equal to those of individuals 15 to 26 years of age who received three doses; Only two doses are needed, 6-12 months apart, if vaccination against HPV begins before the age of 15 in boys and girls [18,21,22]. The 6-month interval between these two doses is critical to ensure adequate immune titers and protection durability. If the interval between the two doses is less than 5 months, a third dose is recommended. In addition to the ability to use two doses instead of three doses, vaccination at earlier ages is preferred, because HPV vaccines are more effective when given prior to exposure to HPV infection, which coincides with beginning of sexual activity [22,23], or in the target age (11-12 years). Nonavalent vaccine can be used

to continue or complete the male series [24]. The nonavalent and quadrivalent vaccines had similar safety profiles except that the nonvalent vaccine had a higher rate of swelling and erythema at the injection site than the quadrivalent HPV vaccine, and the rate increased after each successive dose of HPV Vaccine nonavalent [24]. A person with a moderate or severe febrile illness should wait until the disease improves before receiving a vaccine. The HPV vaccine significantly reduces the incidence of anogenital cancers and genital warts. In addition, vaccination against HPV can reduce the incidence of oropharyngeal cancer, as well as maternal transmission of HPV to infants. Human papilloma virus in infants can result in recurrent laryngeal papillomatosis [18].

The vaccine has been approved in more than 100 countries and is part of the national immunization program in some countries such as the United Kingdom and Australia; it is approved for use in women aged 9 to 26 years, in some countries the age range has been extended to 45 years of age. Both vaccines have a 95% efficacy in preventing persistent infection with HPV-16 or HPV-18 and 100% in preventing SIL when given to girls before the onset of sexual activity or those women without infection of these genotypes; Vaccine protection has durability [18].

The HPV vaccination programs implemented in many developed countries around the world, but these would have greater global impact in developing countries, where the need is greatest, but the high cost of the vaccine prevents their use. In Australia the vaccination program nationwide recombinant quadrivalent HPV vaccine is offered to adolescents 12 to 18 years old, to women under 26 years, with a coverage rate [18,24-27], of 65-75%.

In the UK, HPV vaccination introduced in the national immunization program in 2008 for girls aged 12 to 13 years, and more than 1.4 million doses have been given since the vaccination program started and from 2009 for adolescents 18 years of age or younger; scheme with 3 injections over 6 months, mainly applied in high schools and 80% coverage in adolescents 12 to 13 years, a reduction of 63% of cervical cancer, 51% reduction of CIN-3 is projected and 27% reduction of abnormal smears before 30 years of age [25-28].

Preventive measures against HPV

Condom use is not as effective for the prevention of HPV infection; because the HPV lives in the skin over the pubic area, cells lining the vagina and cervix in women; the urethra and anus in both sexes. Condoms do not block the skin contact of the pubis and therefore not fully protect HPV infection. Reducing HPV infection is the most important measure for preventing cervical cancer reduction; avoid exposure to HPV and HPV vaccination are the best methods of prevention; as HPV infection is spread primarily by sexual contact, sexual abstinence or mutual monogamy reduce the risk of exposure to HPV and condoms only provide 70% protection against HPV when used at all times. Circumcision reduces the risk of penile cancer, urinary tract infections and sexually transmitted infections common, including HIV infection; little information

on the effect of male circumcision on the risk of acquiring HPV infection; but causes genital warts in men and women; besides these, is related to cervical cancer, vulvar cancer, and vaginal cancer in both sexes, anal cancer and penile cancer man. 99% of all cases of cervical cancer are attributable to persistent infection hr-HPV genotypes and factors that reduce the likelihood of acquiring or transmitting infection by HPV in men or women reduces the risk of diseases associated with these infections₂. Consumption by women of three or more times a week; of vegetables and fruits high in beta carotene [2], 40% reduced risk of SIL in relation to non-consumers.

Secondary prevention

Cervical cancer is one of the few common cancers in which has identified a specific causal agent, it is necessary screening and diagnosing women infected with hr-HPV genotypes facilitates close monitoring of those with persistent infection, even in those with normal cervical cytology. In assessing the impact of cytology screening on the incidence and mortality of cervical cancer limitations of cytology. Screening tests should be low tech, providing immediate results (such as direct visual inspection or (DVI) or HPV tests, mainly in regions where transportation and communication technologies are insufficient, the three most useful methods to level world, are DVI, cytology and HPV testing [2,29].

Methods of detection or screening for cervical cancer in developed countries

In developing countries, HPV testing and cytology remain expensive DVI and methods of visual inspection with acetic acid application 3-5% in the cervix and cryosurgery are optimal screening strategy in these countries [29].

Direct visual inspection

Because of the intrinsic problems of screening based on cytology, are developing alternative detection methods, such as methods of direct visual inspection and HPV testing and protocols of alternative management for the prevention of cervical cancer in developing countries, mainly for health services performed in first class by any trained paramedical personnel, anywhere. Detection and treatment does not eliminate the intermediate steps of making colposcopy-directed biopsy for histopathological examination; but reduces the costs and infrastructure needs for the detection increases the compliance of women in their monitoring for detection [2,30].

The first method of visual inspection of the cervix, presented by Schiller in 1930, which used to see Lugol leukoplakia or clinically visible lesions for diagnosis that would otherwise escape the naked eye. This method replaced with cytology because the Schiller test has low specificity; however, studies evaluating the visual inspection of the cervix were resumed; DVI and compared with the performance of cytology and HPV testing; in all studies, test for reference only positive tests were used and only the HSIL were used as outcome measures; DVI using DVI only and cytology; positive results DVI or abnormal

cytology; reference to colposcopy was 18.1% of women and reports regardless of the outcome of DVI or cytology, 97.5% were performed colposcopy; DVI sensitivity for HSIL was 77% higher than cytology was 44%; 64% specificity for DVI in HSIL and 91% for cytology [30]. In women 35-65 years with no history of selected screening using cytology, HPV testing, DVI and cervicography, 18% of positive cases identified DVI 67% of HSIL, 8% of women had LSIL or CIN-1, positive test identified 78% of HSIL; no statistical differences [2,30].

Visual inspection with acetic acid

Visual inspection with acetic acid (VIA), cervicocopy, test and acetic acid test vinegar are some of the names that the DVI known. This test requires a technique: the patient in the supine or lithotomy position to visualize the cervix, vaginal speculum after placement; then clean the cervix with acetic acid 3-5%, it could use spray or cotton swab and observing the cervix with the naked eye or with a simple light suitable view after 1 or 2 minutes, examines the cervix; the presence of areas of acetowhite epithelium is caused by the acetic acid, which is related to the loss of the nuclear-cytoplasmic and these epithelial changes acetic acid ratio, are related from immature squamous metaplasia, infection HPV cervical SIL or cervical cancer precursors. The DVI is different to colposcopy as this examines in more detail the cervix and DVI alone does not determine or injury Acetowhite transformation zone (TZ) of the cervix and classification of positive or not depends Acetowhite injury detection of any area acetowhite different. In their own defined areas observed Acetowhite really TZ, the test is considered positive for precancerous lesions or cervical cancer early. Results are available immediately, allowing treatment in one visit and thus reducing loss to follow up the patient without specialized personnel [2,30]. DVI testing and cytology are similar in specificity when positive. The DVI was positive in 9.8% of women and 10.2% cytology. The DVI identified 90.1% of actual cases and cytology 86.2% true positive cases. Pap tests and DVI are some way equivalent detection tests. The sensitivity of VIA is equivalent or better than cytology, but specificity is lower [31]. The VIA is a sensible alternative method of screening; inexpensive, non-invasive, and is performed in health facilities first class; moreover, the results are immediate, with shipments for the treatment of precancerous lesions by cryotherapy on the same day in the same health center; this method and treat ensures adherence to treatment soon after diagnosis, without problems of not meeting patient referrals. In India the VIA aplicación in women 30 to 59 years 25% reduced the incidence of cervical cancer and 35% mortality [30,31]. Like cytology, VIA is subjective, and need monitoring for quality control of visual inspection methods; VIA have lower performance in postmenopausal women, as the TZ endocervical away in the channel [32], but is useful for follow-up after cryosurgery negative predictive value of 99.7% and specificity of 93.7%, comparable to cytology.

In developing countries, transportation problems, weather and other problems that hinder access monitoring. Through programs and treat, is less likely to be lost during follow-up before being treated and has been evaluated in several countries

with good results as Thailand, Bangladesh, India, South Africa and Ghana, with good results; The VIA and cryosurgery, in one or two clinic visits without colposcopic diagnosis is an alternative or other conventional strategies [32,33].

Visual inspection with Lugol's solution

Visual inspection with Lugol's iodine (VILI) is similar to VIA, but uses Lugol's iodine to map the cervix, followed by a review in the areas of yellow mustard. The detection and treatment can also be done in one visit; studies in India and Africa showed that the sensitivity and specificity for detecting HSIL IVL were 92% and 85%, respectively, in studies of Latin America, IVL had a sensitivity of 53% and specificity of 78% in detecting HSIL; further studies on the accuracy of the IVL is required [2,29].

The most viable and approved WHO strategy for screening for cervical cancer in emerging countries is visual inspection with acetic acid (VIA) or visual inspection with Lugol iodine (VILI). After applying acetic acid or Lugol iodine directly to the cervix, the precancerous and cancerous lesions become white, making them visible to the naked eye. This method has a high sensitivity among HIV-infected and uninfected women. The results are immediate, so women who positively select precancerous lesions receive treatment with cryotherapy during the same visit (screening treatment) is cost effective, affordable, and an ideal first-line treatment for NIC of any grade when size and location Of the cervical lesion allows the cryoprobe to span the entire lesión, can avoid cost burden, follow-up visits, significant delays in treatment and loss of follow-up. Cryosurgery was performed at the primary care level by non-skilled health personnel trained to perform it with minimal equipment [34-39].

Cytology

For decades, cytology been used worldwide to identify precancerous cervical lesions for treatment and monitoring. In developed countries, routine screening with cytology has contributed to the reduction of 70 to 80% of cervical cancer; although one cytology result is not very sensitive for the detection of precancerous lesions. The sensitivity for detecting HSIL varies from 47 to 62% and specificity of 60-95%; one conventional cytology confirmed 40 to 50% of HSIL and cervical cancer in biopsy; failures of cytology results from the sampling technique or process samples. Efforts to improve cytology in this century include the development of liquid-based cytology (LBC), which uses a small amount of liquid to preserve cells collected from the cervix, and automating the process of preparing the smears [2,29].

LBC has high efficiency and reduces laboratory problems like fixing uneven thickness of cell propagation, and air drying artifacts; improves the adequacy of the sample and sensitivity but decreases specificity compared with conventional cytology; also significantly increases the colposcopy sent; taking as reference threshold reporting atypical squamous cells of undetermined significance (ASC-US) (12.7% versus 6.7% in the LBC group compared with conventional cytology, respectively); however, the LBC was more sensitive in detecting HSIL and

cervical cancer. The LBC detected 92.9% of HSIL and 100% of cervical cancer, whereas conventional cytology detected 77.8% of HSIL and 90.9% of cervical cancer [2,29].

Primary cervical cancer screening

HPV testing-hr for the detection and prevention of precursor lesions of cervical cancer Compared to cytology, offering 60 to 70% more protection against cervical cancer, it is more Effective Especially in women 30 to 34 years of age and when to Provides performed every 5 years Greater protection than cytology performed at intervals of 3 years of incorporation hr-HPV testing in developed countries country, has not yet Been determined.; short-term with hr-HPV detection test is inexpensive, and Provide Greater security than conventional cytology; these benefits, public health programs have logistical problems for screening including what kind of hr-HPV test is used to determine Appropriate for ages and screening intervals, management of HPV-positive women hr, ensure quality, addiction and test application programs for the prevention of cervical cancer. The hr-HPV testing is more Effective in detecting HSIL and cervical cancer prevention than cytology in women older than 35 years have proven to be more Also Effective than cytology or VIA and reduced the incidence and mortality from cervical cancer in advanced stages in developing countries [40-49].

Screening tests in developed countries

Early diagnosis and treatment has proven effective in the prevention of cervical cancer; countries with organized screening programs, the incidence rates of cervical cancer decreased; the use of cytologic screening intervals detects precancerous lesions and prevent the development of cervical cancer, reducing their risk up to 80% [2,41]. Many developed countries have significantly reduced the morbidity and mortality from cervical cancer through early detection and treatment of cervical cancer. The success of these countries is largely due to the widespread and systematic use of cytology [2,34]. In the U.S., 90% cytology decreased mortality from cervical cancer; however, half of American women have not been conducted cytology, and cervical cancer diagnosed in 10% of women who have not been performed cytology in the last five years. Australia fell 2.8% annual incidence for cervical cancer with the introduction of screening for cervical cancer in 1991; 85% of Australian women are not regularly take cytology and 50% have never done. The World Health Organization recommends that screening for cervical cancer is initiated in women age 30 or older, is no longer necessary for women 65 years of age or older; every 3 years the range is suitable for women between 25 and 49 years old; Annual cytology has reduced cervical cancer in the past 40 years. The rate of reduction in the incidence of cervical cancer was 64% when the interval between tests was 10 years; with interval of 5 years was 83.6% and 90.8% with 3 years, 92.5% with 2 years and 93.5% annually [14,29].

Discussion

Poverty, as measured by an index of marginalization of the region where women live, is linked to limited access to primary health care, poor accessibility and quality of programs

that use preventive screening tests, resulting in deaths from preventable causes such as cervical cancer 25 to 27 different cultural factors and socioeconomic injustice are inequality causes of health and increased mortality rates from cervical cancer in underserved populations [23–25].

To reduce the high rates of mortality from cervical cancer is necessary to institute measures of innovation and equity; create sex education campaigns, increase screening coverage and provided women with geographical, cultural or economic barriers; free universal application of the HPV vaccine and the full treatment for all women's [26].

An effective program of prevention and control of cervical cancer must address several issues, including the coverage and quality of screening services, availability of diagnosis, treatment and monitoring, reliable and affordable. Ensure the prevention of cervical cancer with the addition of vaccination in public health plans in each country. An effective program for the prevention of cervical cancer must be supported by clearly delineated national strategic policy.

Conclusions

Permanent organized and primary prevention programs and screening are needed to address the global social inequality and reduce mortality rates from cervical cancer.

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